

Insights in paediatric virology during the COVID-19 era (Review)

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Abstract. The present article provides an overview of the key messages of the topics discussed at the ‘7th Workshop on Paediatric Virology’, which was organised virtually on December 20, 2021 by the Institute of Paediatric Virology, located on the Island of Euboea in Greece. The workshop’s plenary lectures were on: i) viral pandemics and epidemics in the ancient Mediterranean; ii) the impact of obesity on the outcome of viral infections in children and adolescents; and iii) COVID-19 and artificial intelligence. Despite the scarcity of evidence from fossils and remnants, viruses have been recognised as significant causes of several epidemics in the ancient Mediterranean. Paediatric obesity, a modifiable critical health risk factor, has been shown to impact on the development, progression and severity of viral infections. Thus, the prevention of paediatric obesity should be included in formulating public health policies and decision-making strategies against emerging global viral threats. During the current COVID-19 pandemic, artificial intelligence has been used to facilitate the identification, monitoring and prevention of SARS-CoV-2. In the future, it will play a fundamental role in the surveillance of epidemic-prone infectious diseases, in the repurposing of older therapies and in the design of novel therapeutic agents

against viral infections. The collaboration between different medical specialties and other diverse scientific fields, including archaeology, history, epidemiology, nutritional technologies, mathematics, computer technology, engineering, medical law and ethics is essential for the successful management of paediatric viral infections. The current COVID-19 pandemic has underscored this need, which should be further encouraged in modern medical education.

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1. Introduction

The ‘7th Workshop on Paediatric Virology’ was held virtually, due to the current coronavirus disease 2019 (COVID-19) pandemic, on December 20, 2021. The workshop was organised by the Institute of Paediatric Virology, which is located on the Island of Euboea in Greece (1) (for further information about the Institute of Paediatric Virology please visit its official website at <https://paediatricvirology.org>). The workshop was chaired by Dr Simon B. Drysdale, Consultant and Honorary Senior Lecturer in Paediatric Infectious Diseases at St. George’s University Hospital NHS Trust and St. George’s University of London, UK (Chair of the ‘7th Workshop on Paediatric Virology’) and Professor Anna Kramvis, Research Professor of Molecular Virology at the University of the Witwatersrand

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in Johannesburg, South Africa (Honorary Chair of the ‘7th Workshop on Paediatric Virology’). Dr John Papadatos, former Clinical Director and Consultant Paediatric Intensivist at the ‘Aglaia Kyriakou’ Children’s Hospital in Athens, Greece, was awarded with the ‘2021 George N. Papanicolaou Humanitarian Award’ for his contribution in founding paediatric intensive care in Greece (2). Mrs. Vassiliki Rabaouni, High School Teacher of Hellenic Literature at the ‘Zosimaia’ School of Ioannina, Greece and Coordinator during the academic year 2020-2021 of the High School educational programme entitled ‘From ‘nouson kakion’ of Homer to COVID-19’ (‘Από την ‘νοῦσον κακήν’ του Ομήρου στον COVID-19’), was also awarded with the ‘2021 Paediatric Virology Award’ for her contribution to teaching high school students about severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (for further information on ‘Zosimaia’ School of Ioannina please visit: <https://gym-zosim.ioa.sch.gr/>).

The aim of the present review article is to provide an overview of the key messages of the plenary lectures presented at the ‘7th Workshop on Paediatric Virology’. The topics, which were covered during the workshop, were the following: i) Viral pandemics and epidemics in the ancient Mediterranean; ii) the impact of obesity on the outcome of viral infections in children and adolescents; and iii) COVID-19 and artificial intelligence (Table I).

2. Viral pandemics and epidemics in the ancient Mediterranean: An overview

As the world begins to emerge from the devastation of COVID-19, it is useful to remember that this is not the first pandemic that human beings have survived. The ancient world suffered through numerous pandemic and epidemic events, some of which are lost to history. However, there is historical evidence of several epidemics and pandemics, particularly in the ancient Mediterranean. The evidence for these diseases comes from a number of sources. First, of course, are the surviving ancient writings, from physicians such as Hippocrates, Galen and Dioscorides (3). The most extensive descriptions of infectious diseases, including viral epidemics, are derived from the ‘Hippocratic Corpus’ written by Hippocrates, who reported the ‘cough of Perinthos’ epidemic, an influenza-like outbreak in the 5th century B.C., and discussed in detail several cases complicated with pneumonia or fatal outcome (4,5). Poets, ancient historians, philosophers and general scientists, such as Homer, Aristotle, Thucydides, Theophrastus, Lucretius and Pliny all contributed to the current knowledge of the symptoms and social impacts of epidemics; however, the identification of specific diseases is impeded by their perspectives on the cause of diseases, which frequently obscure the clear description of the symptoms (6).

With a few historical exceptions, for the identification of ancient epidemics, one must turn to the physical remains of the victims. Mass burials or hastily constructed graves provide information of catastrophic mortality events, and in the absence of evidence for trauma, epidemics are usually suspected. Moreover, unless the patient survives for several weeks, few diseases leave evidence on bones, and the majority of these diseases are bacterial, rather than viral. The mycobacterial diseases, leprosy and tuberculosis, have a particular affinity for bone in patients with chronic disease, and produce

distinctive changes to the skeleton; these are almost never diagnosed with a degree of certainty, but rather represent the most probable cause of the preserved lesions (7-9). Bacteria are the source of the more well-known historical epidemics, including the Plague, which first appeared in the reign of the Roman emperor Justinian and was caused by *Yersinia pestis* (10,11).

Viral epidemics are more elusive, as few viruses directly affect bones in a manner that can lead to gross lesions (8). When lesions are present, it is difficult to identify the cause. Otitis and meningoencephalitis can produce endocranial lytic lesions in the cranial vault and petrous temporals; both diseases are described in the Hippocratic writings; however, the specific infectious agent remains unknown (5). Lesions and bone formation on the pleural surfaces of ribs are considered to be caused by infections, usually bacterial or viral, although fungi, renal disease, cancer and trauma may all be responsible, thus rendering the identification of the causal agent more complex (12).

Developments in the recovery and identification of ancient pathogen DNA have facilitated the identification of viral diseases. Smallpox (*Variola*) periodically entered the Mediterranean countries as early as the Bronze Age (13). The mummy of Pharaoh Ramses V (died in 1157 BC) exhibits the characteristic skin lesions of smallpox, and variola virus DNA has been recovered from his remains (5). Smallpox is also one of the strong candidates for the cause, or one of the causes, of the well-known 5th century BC ‘Plague of Athens’ described by Thucydides (14). To date, only typhoid fever has been identified in a small number of samples obtained from a mass grave considered to be associated with the event (15,16); but typhoid would have been endemic and is unlikely to have caused the catastrophic infections in all age groups described by Thucydides (14). Although smallpox reappeared over millennia in the Eastern Mediterranean, populations were almost certainly small enough that it would die out completely after a few years. As a result, subsequent introductions of the disease would find a population in which no one had any immunity, with devastating effects each time (17).

Ancient writers describe the effects of other viral diseases that can be tentatively identified as poliomyelitis, chicken pox, shingles, hepatitis, mumps, herpes and others (3,6). The majority of diseases have no skeletal symptoms, although limb paralysis from poliomyelitis has been tentatively identified through atrophied and shortened leg bones, while histology and advanced imaging techniques have been shown to aid in the diagnosis of less grossly obvious specimens (18). However, as the recovery and amplification techniques for viral DNA improve and the analyses become both more affordable and common, it can be anticipated that diseases that lack skeletal symptoms may finally be identified; thus, more in-depth knowledge of the history of viral diseases in the Mediterranean may be acquired.

3. The impact of obesity on the outcome of viral infections in children and adolescents

The association between obesity and viral infections has been studied for a number of years and in particular during the 2009 H1N1 influenza pandemic, when obese patients were considered at an increased risk of influenza-related complications, a longer intensive care unit (ICU) stay and a higher

Table I. The top key messages of the '7th Workshop on Paediatric Virology' organised virtually by the Institute of Paediatric Virology.

<p>Viral epidemics in the ancient Mediterranean</p>	<p>The most extensive descriptions of infectious diseases in ancient Greece, including viral epidemics, are derived from the 'Hippocratic Corpus' written by Hippocrates, who reported the 'cough of Perinthos' epidemic in the 5th century BC. Smallpox is a strong candidate for the cause, or one of the causes, of the well-known 5th century BC 'Plague of Athens' described by Thucydides. Developments in the recovery and identification of ancient pathogens' genomes are expected to facilitate the identification of several viral diseases.</p>
<p>Viral infections and obesity</p>	<p>The world is currently in the middle of two pandemics that have unfortunately collided: Paediatric obesity has undergone an unprecedented increase over the past decades with exponential rates during the COVID-19 pandemic. The present review of real-world data demonstrated that obese children and adolescents have more severe outcomes in viral infections.</p>
<p>COVID-19 and AI</p>	<p>AI technology models can be of tremendous help during the ongoing COVID-19 pandemic. The use of AI can easily track the spread of SARS-CoV-2, identify high-risk patients, control the infection in real-time, predict mortality risk by adequately analysing previous data of patients, fight against the virus by population screening, medical help, notification and suggestions about infection control, improve the planning, treatment and reported outcomes of COVID-19 and reduce the workload of healthcare workers. AI can be very useful in drug delivery design and development, identifying useful molecules at a much faster rate than usual and is also helpful for clinical trials. However, such use of information and big data raise ethical, legal and constitutional issues that have to be carefully evaluated in order protect humanity and human rights.</p>
<p>COVID-19, coronavirus disease 2019; AI, artificial intelligence; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.</p>	

mortality (19,20). Moreover, there is increasing evidence that the immune response of obese patients is also impaired in other viral infections, such as dengue and respiratory viruses, including the current SARS-CoV-2 pandemic strain. As data are limited and conflicting regarding the paediatric population, the present study aimed to systematically review the impact of obesity on the outcome of viral infections of interest in order to provide insight into the prognosis and early treatment of this subset of patients.

In the context of the '7th Workshop on Paediatric Virology', Dr Patra Koletsi and Dr Dimitra-Irinna Vitoratou systematically reviewed published studies reporting on obesity or body mass index (BMI) and their association with the outcome of viral infections (21-40). PubMed was searched for articles published up to August 30, 2021, using the following terms: (obesity OR BMI OR metabolic syndrome) AND (viral infection OR virus* OR influenza OR COVID-19 OR SARS-CoV-2) AND (child OR adolescent). The PROSPERO registry was searched for relevant review articles. The citations of selected articles and relevant review articles were manually searched. Subsequently, the two reviewers (PK and DIV) independently screened the abstracts of the retrieved articles. From each article included in the review, the following data were recorded: The study design, study population number, age, country and month/year of enrolment. In studies that included adult populations, the data referring to children and adolescents were extracted. Conversely, studies reporting on respiratory syncytial virus (RSV) including toddlers and infants <2 years old were excluded, as obesity is not a well-defined pathological condition in this subset of patients.

Among the 2,278 citations initially retrieved from PubMed, 19 studies were identified as eligible for inclusion in the review. The flow chart for the process of selection of included studies in the review is illustrated in Fig. 1. The majority of studies used the standard World Health Organization (WHO) or Centers for Disease Control and Prevention (CDC) criteria to define obesity (see <https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight> and <https://www.cdc.gov/obesity/childhood/defining.html>, respectively). According to the WHO, for children <5 years of age, obesity is considered when the weight-for-length/height score is >3 standard deviations above the WHO Child Growth Standards median (charts available at: https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-length-height/cht-wflh-boys-z-0-5.pdf?sfvrsn=6bcd4d28_11; and https://cdn.who.int/media/docs/default-source/child-growth/child-growth-standards/indicators/weight-for-length-height/cht-wflh-girls-z-0-5.pdf?sfvrsn=7abd186d_9; for boys and girls, respectively). For children aged between 5-19 years, obesity is considered when the z-score is >2 standard deviations above the WHO Growth Reference median (charts available at: [https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/bmi-for-age-\(5-19-years\)/bmifa-boys-z-5-19-labels.pdf?sfvrsn=5775aced_4](https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/bmi-for-age-(5-19-years)/bmifa-boys-z-5-19-labels.pdf?sfvrsn=5775aced_4); and [https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/bmi-for-age-\(5-19-years\)/bmifa-girls-z-5-19-labels.pdf?sfvrsn=94b20617_4](https://cdn.who.int/media/docs/default-source/child-growth/growth-reference-5-19-years/bmi-for-age-(5-19-years)/bmifa-girls-z-5-19-labels.pdf?sfvrsn=94b20617_4); for boys and girls, respectively). According to the CDC, for a child >2 years of age, obesity is defined as a BMI \geq 95th percentile of the CDC sex-specific BMI-for-age growth charts (charts available at: [\[cdc.gov/growthcharts/data/set1clinical/cj41c023.pdf\]\(https://www.cdc.gov/growthcharts/data/set1clinical/cj41c023.pdf\); and <https://www.cdc.gov/growthcharts/data/set1clinical/cj41c024.pdf>; for boys and girls, respectively\). BMI is calculated by dividing the weight of an individual in kg by the square of height in meters.](https://www.</p>
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The data extracted from each of the included studies are presented in Table II. As regards COVID-19, three out of four studies with a total population aged <22 years of >44,000, identified obesity as a significant risk factor for severe disease and subsequent hospitalization (21-24). That said, a surveillance study from Mexico (23) found a significant association with progression to pneumonia only when combined with patients diagnosed with type 2 diabetes. All three observational studies on multisystem inflammatory syndrome in children (MIS-C) found a high prevalence of obesity among paediatric patients of >25%. However, the lack of cross-sectional design does not allow for firm conclusions to be drawn. Likewise, among the eight influenza and influenza-like illness (ILI) studies included in the review, four studies (28,31,33,35) revealed an unfavourable outcome for disease severity, the risk of hospitalization and mortality, while the other four (29,30,32,34) did not demonstrate a significant impact of obesity among children and adolescents. Furthermore, obesity was associated with a greater number of days of wheezing, fever and drip infusion in RSV infection in toddlers and preschool children (36), and higher odds of developing severe dengue infection (39). Finally, two studies were identified referring to chronic hepatitis C, where obesity was significantly associated with progression to liver fibrosis and impaired sustained virologic response to treatment (37,38).

The literature review demonstrated the unfavourable implication of obesity on the outcome of respiratory, as well as vector- and blood-borne infectious diseases in children and adolescents. Translational studies have indicated that obesity is characterized by chronic low-grade inflammation with a disrupted balance between pro- (e.g., IL-6, TNF- α , IL-1 β and leptin) and anti-inflammatory (e.g., IL-10 and adiponectin) cytokines, leaning towards an overall pro-inflammatory state (40-42). Cardiovascular changes in obesity, such as left heart hypertrophy and high blood pressure, that lead to endothelial injury, have been recognized even in very young children. Specifically, for COVID-19, human post-mortem studies have demonstrated the inclusion of coronavirus particles in endothelial cells, possibly via the angiotensin-converting enzyme 2 receptors, as well as the accumulation of inflammatory cells, pulmonary venous congestion and intestinal endothelial inflammation (42,43). Leptin, the levels of which are usually elevated in obese patients, damages the endothelium, leading to less nitric oxide production and modulates the innate and adaptive immune response leading to inflammation aggravation. Furthermore, obese children and adolescents appear to have higher influenza viral loads in exhaled droplets compared with their leaner counterparts and shed the virus for longer periods of time (42).

Similarly, adiponectin, the levels of which are reduced in obese patients, has been demonstrated to exert a protective effect against Fas-mediated hepatocyte death (37,38). This subsequently affects regulatory processes, which are critical in inflammatory and immune responses that drive the outcome in hepatitis C virus infection (38). Finally, in obese patients with

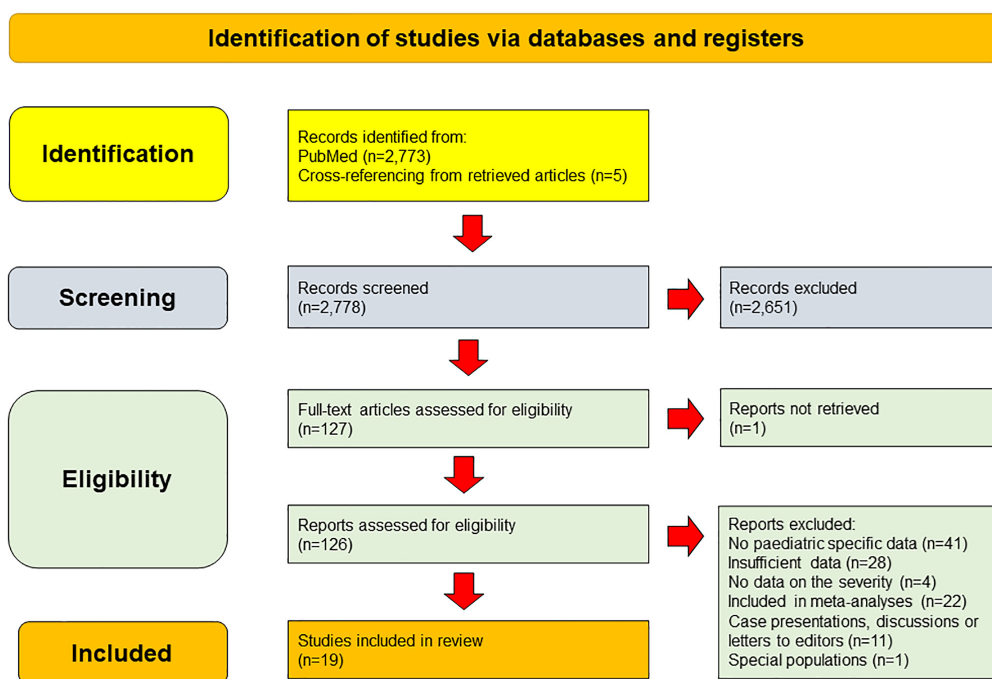


Figure 1. Flow chart of the process of the selection of articles on the impact of obesity on the outcome of viral infections for inclusion in the present review article.

dengue infection, the increased production of IL-6, IL-8 and TNF- α by adipose tissue increases capillary permeability, which further contributes to the process of severe plasma leakage (39). Given the substantial increase in obesity rates in children during the current pandemic induced by the prolonged quarantine durations and the reduced physical activity, public health policies need to be urgently redirected to the prevention of excess weight gain in children. Improving the metabolic health and immunity of children may be an effective preventive measure for counteracting the consequences of viral infectious diseases.

4. COVID-19 and artificial intelligence

SARS-CoV-2 has caused an unprecedented pandemic viral threat globally, which is still in progress (44-47). To date, it has affected human life in several aspects, not only through the loss of millions of individuals worldwide, but also through the implementation of unprecedented and particularly strict measures that modern societies could never have conceived. For the first time, in a time of peace, the Olympic Games were postponed. However, such decisions have a marked impact on economic, educational, psycho-emotional and social levels, causing an additional worldwide crisis, the results of which may have not yet been fully observed.

The early identification of infected individuals, whether they are in the pre-symptomatic, asymptomatic or symptomatic stage, their isolation by monitoring their health and the simultaneous search and isolation of their close contacts has proven to be the cornerstone of dealing with the pandemic, as there are only a limited number of effective treatments available thus far (48-52). In addition, due to shortages in medical

and nursing staff and infrastructure, it is absolutely necessary to select the most suitable patients who require clinical and/or laboratory examination, hospitalization or admission to the ICU. In this area, the contribution of technology through the use of artificial intelligence (AI) models, may be of great assistance (48,51,53). In addition, the use of technology has played a crucial role in the search for appropriate therapeutic substances, as well as in the development of vaccines, at a rate at which has not been previously observed (54,55).

At the beginning of the SARS-CoV-2 pandemic in China, AI programs were used to identify and track infected individuals or those with a travel history to a high-risk area (via face recognition with thermal cameras), robots were tasked to transport food and medicine to enclosed areas, while drones were used to patrol persons under quarantine, transmit messages that urged individuals to stay home and also disinfect certain public areas (56). In addition, cell phone data, debit and credit card transactions (tracking down infected individuals or quarantine cases), popular internet searches and social media posts can all provide information on the epidemiology of numerous communicable diseases. Korea successfully dealt with the transmission of the virus without the imposition of bans by using such data (50). Another good example is *BlueDot* software (Canadian surveillance platform <https://bluedot.global/healthcare/>) that uses an AI algorithm with data from the issuance of airline tickets worldwide, which issued a warning for the onset of COVID-19 on December 31, 2019, the same time as the clinical detection of the first cases (57). On the other hand, specific attention should be paid to the processing of the information ‘storm’ that can be collected, in order to avoid any adverse results, such as misinformation or propaganda or issues with privacy (53).

Table II. Characteristics of studies included in the narrative review on the impact of obesity on the outcome of viral infections.

Authors/(Refs.), year	Study design	Setting: N; age range; study population; country; month/year of enrolment	% Obesity in studied populations ^a	Outcome
COVID-19				
Kompaniyets (21), 2021	Cross-sectional	43,465 patients ≤18 years, USA (900 geographically dispersed USA hospitals; 03/2020-01/2021)	2.5%	Strong risk factor for hospitalization (aRR, 3.07; 95% CI, 2.66-3.54), but not for severe COVID-19 infection
Tsankov <i>et al</i> (22), 2021	Meta-analysis and systematic review (cross-sectional sub-analysis)	6 of 42 studies referring to 275,661 patients <21 years of age without and 9,353 children with comorbidities; international; 01/2020-10/2020	NA	Obese children had a higher relative RR for severe COVID-19 and associated mortality compared to children without co-morbidities (RR, 2.87; 95% CI, 1.16-7.07; I ² =36%)
Moreno-Noguez <i>et al</i> (23), 2021	Retrospective surveillance study	1,443 patients with COVID-19 <19 years old; Mexico; 12/2019-03/2020	5.7%	Obesity not shown to be a significant risk factor for COVID-19 pneumonia; however, the combination of obesity/type-2 diabetes yielded an OR of 2.9 (OR, 2.9; 95% CI, 1.75-4.95)
Webb and Osburn (24), 2021	Retrospective case series	163 patients with COVID-19 <22 years old; California; 05/2020-09/2020	27%	Significant association for obesity: 19% of incidentally infected and 22% of potentially symptomatic were obese vs. 60% of significantly symptomatic patients (P=0.001)
MIS-C				
Abrams <i>et al</i> (25), 2021	Retrospective surveillance study (CDC MIS-C database)	1,080 patients <21 years old; USA; 03/2020-10/2020	26%	29.2% of patients admitted to the ICU were obese compared to 22% that were not admitted; obesity was linked to decreased cardiac function (aOR, 1.4; 95% CI, 1.0-1.9) and further ICU admission
Bautista-Rodriguez <i>et al</i> (26), 2021	Retrospective web-based data review of case series	183 patients ≤18 years old; age range, 2.3-11.7 years; international; 03/2020-06/2020	26.2% (most common co-morbidity)	There was no difference in obesity rates between the groups that presented with KD-like presentation, incomplete KD-like presentation or shock presentation (P=0.57)
Hoste <i>et al</i> (27), 2021	Systematic review	953 patients with MIS-C, age range, 0-21 years; 12/2019-08/2020	25.3%	4/18 (22.2%) among fatal cases were obese
Influenza/ILI				
Moser <i>et al</i> (28), 2019	Observational cohort	1,530 patients <19 years old with influenza or ILI; Mexico; 04/2010-03/2014	6.4%	Obese paediatric participants were more likely to develop severe ILI compared to their counterparts with a normal z-score (OR, 2.2; P=0.002); no significant interactions between BMI and different pathogen groups (influenza H1N1, H3N2 and B, coronavirus, metapneumovirus, parainfluenza, and rhinovirus, RSV)

Table II. Continued.

Authors/(Refs.), year	Study design	Setting: N; age range; study population; country; month/year of enrolment	% Obesity in studied populations ^a	Outcome
Neyer <i>et al</i> (29), 2018	Retrospective	188 children with severe influenza complications; USA; age range, 2-20 years; 08/2010-06/2013	8%	The association between severe obesity and known high-risk condition (e.g., asthma, pneumonia, diabetes) for influenza complications (hospitalization or mortality) was not significant (P=0.61)
Bagdure <i>et al</i> (30), 2010	Retrospective	80 of 301 children < 18 years of age admitted to the ICU for severe 2009 H1N1 influenza; USA; 05/2009-11/2009	19%	Obesity was not associated with ICU admission (P=0.45)
Okubo <i>et al</i> (31), 2018	Retrospective	27,781 children <18 years of age hospitalized with bronchitis or pneumonia and influenza, Japan; 07/2010-03/2015	9.9%	Obese patients were younger (P<0.001), more likely to be male (P<0.001), more likely to be hospitalized in winter, and more likely to be treated with antivirals (P<0.001) than underweight, normal weight or overweight children; no association was found between obesity and the likelihood of ICU admission, mean total costs of hospitalization or length of hospital stay
Morgan <i>et al</i> (32), 2010	Case-cohort	11,660 patients with 2009 H1N1 influenza vs. 71,228 controls; age range, 2-19 years; USA; 05/2009-07/2009	16.4%	No association was found between being obese and hospitalization among those with or without chronic medical conditions (OR, 2.2; 95% CI, 0.4-13.4; P=0.4); no association between BMI category and mortality (OR, 0.5; 95% CI, <0.01-68; P=0.81) for children with or without chronic medical conditions
Yu <i>et al</i> (33), 2011	Retrospective	3,577 patients with 2009 H1N1 influenza; age range, 2-17 years; China; 09/2009-02/2010	12%	The proportion of individuals with obesity was significantly higher among patients with severe illness (patients admitted to the ICU) than among case patients with non-severe illness (OR, 1.34; 95% CI, 1.10-1.63; P=0.004); the proportion of individuals with obesity was higher among patients with non-severe illness than among the general population (18% vs. 2%; OR, 10.45; 95% CI, 9.49-11.52)
Gill <i>et al</i> (34), 2015	Review and meta-analysis	5 of 27 studies including 1,782 children with influenza or ILL; age range, 0-19 years; 1980-2010	19%	Obesity was not a risk factor for hospital admission (OR, 0.99; 95% CI, 0.61-1.62)
Garcia <i>et al</i> (35), 2015	Retrospective	696 children with 2009 H1N1 influenza; age range, 0-18 years; Texas, USA; 04/2009 -06/2010	1.9% (probably under-reported)	Obesity was associated with greater disease severity (aOR, 3.28; 95% CI, 1.05-10.21; P=0.04)

Table II. Continued.

Authors/(Refs.), year	Study design	Setting: N; age range; study population; country; month/year of enrolment	% Obesity in studied populations ^a	Outcome
RSV infection				
Akiyama <i>et al</i> (36), 2011	Retrospective	243 patients with RSV bronchiolitis or pneumonia, age range, 1-6 years; Japan; 01/2000-12/2008	NA	When the obesity ratio ^b was ≤ 6 , the days of wheezing exhibited a significant negative association with obesity ratios (OR, 0.13; 95% CI, -0.21-0.05; P=0.001); when the obesity ratio was >6 , the days of wheezing (OR, 0.19; 95% CI, 0.06-0.31; P=0.004), days of fever after admission (OR, 0.07; 95% CI, 0.01-0.14; P=0.021) and days of drip infusion (OR, 0.15; 95% CI, 0.07-0.24; P=0.001) exhibited a significant positive association with obesity ratios
HCV Infection				
Pokorska-Śpiewak <i>et al</i> (37), 2015	Retrospective	42 children with chronic hepatitis C infection; age range, 7-14.4 years; Poland; 2002-2013	17%	BMI z-score was independent positive predictor of progression to liver fibrosis (P=0.03); BMI was not associated with the presence of lymphoid aggregates or steatosis
Delgado-Borrego <i>et al</i> (38), 2010	Retrospective	123; age range, 4.6-19.8 years; Boston, MA, USA; 06/1993-06/2007	Overweight and obese (29.3%)	The presence of steatosis was significantly associated with higher mean (\pm SE) BMI percentiles [72nd (± 5.8) vs. 58th (± 3.5) percentile, P=0.04]; non-responders to treatment had a higher mean (\pm SE) BMI percentile (70th ± 7.4) when compared to responders (50th ± 6.5) in univariate and multivariate analyses (P=0.04 and P=0.02, respectively); one standard deviation increase in baseline BMI z-score is associated with a 12% decrease in the probability of a sustained virological response
Dengue virus				
Zulkpli <i>et al</i> (39), 2018	Review and meta-analysis	15 studies, 7,133 patients; age range, 0-18 years with dengue fever; international; 2000-2016	NA ^c	38% higher odds of developing severe dengue infection among obese children compared to non-obese children (OR, 1.38; 95% CI, 1.10-1.73; P=0.01; I ² =36.7%)

The abstracts of all selected studies were analysed by PK and DIV. ^aUnless specified otherwise; ^bobesity ratio: [(observed body weight-standard body weight of age and sex)/standard body weight of age and gender x100]; ^ccertain studies also included overweight and patients with over-nutrition. COVID-19, coronavirus disease 2019; aRR, adjusted risk ratio; CI, confidence interval; NA, not available; RR, risk ratio; OR, odds ratio; MIS-C, multisystem inflammatory syndrome in children; CDC, Centers for Disease Control and Prevention; ICU, intensive care unit; aOR, adjusted odds ratio; KD, Kawasaki disease; ILI, influenza-like illness; BMI, body mass index; RSV, respiratory syncytial virus; HCV, hepatitis C virus; SE, standard error; NA, data not available.

AI technology includes machine learning (ML) and deep learning (DL). Through smart devices, it imitates human intelligence and the processing of the human spirit, based on algorithms (51). ML, a subtype of AI, applies mathematical models (statistics) to examples and data and recognizes patterns in the information gathered in order to draw future conclusions, without prior knowledge or specific planning, while DL is the most tangible manifestation of ML, which exploits artificial neural networks and functions, similar to a model of human cognitive function (51,52). AI-based technologies, using patients' personal health data, create cognitive datasets that help clinicians in decision-making and in the planning of personalized care for patients (54). They can aid in the early identification of diseases and epidemics, and predict the mode of transmission and probable outbreaks in different geographical areas. They have been used in the past for the diagnosis of tuberculosis, using the artificial immune recognition system (ARIS), as well as in the diagnosis of malaria, and of the Ebola and Zika viruses; however, they have also contributed to the treatment of previous epidemics of other coronaviruses, such as the one causing SARS in 2003 and the Middle East respiratory syndrome in 2012, using the autoregressive integrated moving average (ARIMA) system. The collaboration of King's College London (London, UK) with Massachusetts General Hospital (Boston, MA, USA) created an AI tool for COVID-19 symptom tracker on smartphones that among others, recognized the onset of anosmia as an early sign of COVID-19 (58). At the onset of the pandemic on January 22, 2020, Johns Hopkins University (Baltimore, MA, USA), and in particular the Centre for Science and Engineering, published a toolbar (<https://www.arcgis.com/apps/dashboards/bda7594740fd40299423467b48e9ecf6>) that located, with accuracy, reported cases of COVID-19 in real-time, contributing to the timely identification of new cases, proposing remedial measures (e.g., quarantine) and informing travellers in these areas (59).

Such use of information though, raises ethical, legal and constitutional issues. Currently, it is crucial that researchers, law professionals and technocrats work together to create a secure framework for processing the sensitive personal data of each citizen, so that the progress of technology is not hindered and individual freedom is guaranteed.

5. Conclusions and future perspectives

The '7th Workshop on Paediatric Virology' not only brought together researchers and clinical scientists from Greece, Canada, South Africa and the UK, but also addressed crucial and relevant issues in the rapidly increasing educational field of paediatric virology. Epidemics and pandemics are not new to humankind, having been documented in ancient cultures, including the ancient Mediterranean era. New technologies, such as next-generation sequencing on DNA extracted from fossils, may provide tools for the retrospective identification of the role of viruses in ancient pandemics. Paediatric obesity, which has been aggravated by the COVID-19 pandemic, poses a critical risk factor, impacting on the development, progression and severity of viral infections. Therefore, weight management in children may prove to be an important preventive measure against viral infections in formulating public health policies and decision-making strategies. During the current COVID-19

pandemic, AI has been used to facilitate the identification, monitoring and prevention of SARS-CoV-2. In the future, it will play a fundamental role in surveillance of epidemic-prone infectious diseases, repurposing of older therapies and computer-aided design of new therapeutic agents against viral infections. The current COVID-19 pandemic has highlighted the need for collaboration between different medical specialties as well as between diverse scientific fields, including archaeology, history, epidemiology, nutritional technologies, mathematics, computer technology, engineering, medical law and ethics. This need should definitely be encouraged in modern medical education.

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Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

INM, MT and DAS are co-founders of the Institute of Paediatric Virology. ML, PK, DIV, CK, AP, HK, AK and SBD declare that they have no competing interests.

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